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Patent and Trademark Office

20022

SEARCH REQUEST FORM

Examiner # (Mandatory): K. Weddington Requester's Full Name: _____

Art Unit 1614 Location (Bldg/Room#): CM1 2A17 Phone (circle 305 306 308) 4650

Serial Number: 08/804,903 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention Method and Composition for Treatment of Diabetes

Inventors (please provide full names): Robert R. Rieveley

Earliest Priority Date: 2-24-97

Keywords (include any known synonyms registry numbers, explanation of initialisms):

The insulin sensitizer is selected from

BRL 49653
~~Rx~~ Troglitazone HCL
Troglitazone
MC 555
ALRT 215
CGD 1064

Chroman Predicate
V-411
Vinyldyl Sulfide
Chromic Polynitrate

1042
1003-13
23
33
43

Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

A method for the treatment of diabetes mellitus with a composition comprising

a) an insulin sensitizer

b) a drug selected from

1) an orally ingestible insulin
2) an injectable insulin
3) a sulfonylurea
4) a biguanide
5) an alpha-glucosidase inhibitor

SCA F369

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258

STAFF USE ONLY

Searcher: Mary

Searcher Phone #: _____

Searcher Location: _____

Date Picked Up: 4/29/99

Date Completed: _____

Clerical Prep Time: _____

Terminal Time: 39

Number of Databases: _____

Type of Search

_____ N.A. Sequence
_____ A.A. Sequence
_____ Structure (#)
_____ Bibliographic
_____ Litigation1
_____ Fulltext
_____ Procurement
_____ Other

Vendors (include cost where applicable)

$160.83 STN
_____ Questel/Orbit
_____ Lexis/Nexis
_____ WWW/Internet
_____ In-house sequence systems (list)
_____ Dialog
_____ Dr. Link
_____ Westlaw
_____ Other (specify)

=> s ("brl-49653" or "dioglitazone hcl" or troglitazone or "mc 555" or "alrt 268" or "lgd 1069" or chronic dicolinate or "v-411" or vanadyl sulfate or chronic polynicotinate)/cn

Weddington
804903

```
                0 "BRL-49653"/CN
                0 "DIOGLITAZONE HCL"/CN
                1 TROGLITAZONE/CN
                0 "MC 555"/CN
                0 "ALRT 268"/CN
                1 "LGD 1069"/CN
                0 CHRONIC DICOLINATE/CN
                0 "V-411"/CN
                0 VANADYL SULFATE/CN
                0 CHRONIC POLYNICOTINATE/CN
L1              2 ("BRL-49653" OR "DIOGLITAZONE HCL" OR TROGLITAZONE OR "MC 555"
OR                OR "ALRT 268" OR "LGD 1069" OR CHRONIC DICOLINATE OR "V-411"
                  VANADYL SULFATE OR CHRONIC POLYNICOTINATE)/CN
```

=> fil medl,caplus,biosis,embase,wpids

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	46.30	46.45

FILE 'MEDLINE' ENTERED AT 10:25:31 ON 29 SEP 1999

FILE 'CAPLUS' ENTERED AT 10:25:31 ON 29 SEP 1999
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'EMBASE' ENTERED AT 10:25:31 ON 29 SEP 1999

FILE 'WPIDS' ENTERED AT 10:25:31 ON 29 SEP 1999

=> s ("brl-49653" or "dioglitazone hcl" or troglitazone or "mc 555" or "alrt 268" or "lgd 1069" or chronic dicolinate or "v-411" or vanadyl sulfate or chronic polynicotinate or l1) and diabet?

```
L2          308 FILE MEDLINE
L3          314 FILE CAPLUS
L4          372 FILE BIOSIS
L5          619 FILE EMBASE
L6           12 FILE WPIDS
```

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TOTAL FOR ALL FILES
L7        1625 ("BRL-49653" OR "DIOGLITAZONE HCL" OR TROGLITAZONE OR "MC 555"
               OR "ALRT 268" OR "LGD 1069" OR CHRONIC DICOLINATE OR "V-411"
OR
               VANADYL SULFATE OR CHRONIC POLYNICOTINATE OR L1) AND DIABET?

=> s l7 and (oral? ingest? or inject? or sulfonylurea or biguanide or
glucosidase inhibit?)

L8          73 FILE MEDLINE
L9          88 FILE CAPLUS
L10         59 FILE BIOSIS
L11        217 FILE EMBASE
L12          2 FILE WPIDS

TOTAL FOR ALL FILES
L13        439 L7 AND (ORAL? INGEST? OR INJECT? OR SULFONYLUREA OR BIGUANIDE
               OR GLUCOSIDASE INHIBIT?)

=> s l13 and mellit?

L14         67 FILE MEDLINE
L15         56 FILE CAPLUS
L16         34 FILE BIOSIS
L17        205 FILE EMBASE
L18          2 FILE WPIDS

TOTAL FOR ALL FILES
L19        364 L13 AND MELLIT?

=> s rieveley r?/au,in and l19

'IN' IS NOT A VALID FIELD CODE
L20          0 FILE MEDLINE
L21          0 FILE CAPLUS
L22          0 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L23          0 FILE EMBASE
L24          0 FILE WPIDS

TOTAL FOR ALL FILES
L25          0 RIEVELEY R?/AU,IN AND L19

=> s l19 and sensitiz?

L26         10 FILE MEDLINE
L27         12 FILE CAPLUS
L28          5 FILE BIOSIS
L29         16 FILE EMBASE
L30          0 FILE WPIDS

TOTAL FOR ALL FILES
L31         43 L19 AND SENSITIZ?

=> dup rem l31

PROCESSING COMPLETED FOR L31
L32          31 DUP REM L31 (12 DUPLICATES REMOVED)

=> d tot all
```

L32 ANSWER 1 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:81575 CAPLUS
DN 130:134189
TI Treatment of **diabetes** with a thiazolidinedione, an insulin secretagogue, and an .alpha.-**glucosidase inhibitor**
IN Buckingham, Robin Edwin; Smith, Stephen Alistair
PA Smithkline Beecham PLC, UK
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-64
ICS A61K031-70; A61K031-715; A61K031-64; A61K031-715; A61K031-70
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9903478	A1	19990128	WO 1998-GB2112	19980716
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9884490	A1	19990210	AU 1998-84490	19980716

PRAI GB 1997-15298 19970718
WO 1998-GB2112 19980716

AB A method and compn. are disclosed for the treatment of **diabetes mellitus** and conditions assocd. with **diabetes mellitus** in a mammal. The method comprises administering an effective nontoxic and pharmaceutically acceptable amt. of an insulin **sensitizer**, an insulin secretagogue and an .alpha.-**glucosidase inhibitor** antihyperglycemic agent to a mammal in need thereof.

ST thiazolidinedione insulin secretagogue alpha **glucosidase inhibitor** antidiabetic; **sensitizer** secretagogue insulin alpha **glucosidase inhibitor** antidiabetic

IT Antidiabetic agents
Drug delivery systems
Tablets (drug delivery systems)
(thiazolidinedione, insulin secretagogue, and .alpha.-**glucosidase inhibitor** for **diabetes** treatment)

IT **Sulfonylureas**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinedione, insulin secretagogue, and .alpha.-**glucosidase inhibitor** for **diabetes** treatment)

IT 9001-42-7, .alpha.-**Glucosidase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; thiazolidinedione, insulin secretagogue, and .alpha.-**glucosidase inhibitor** for **diabetes** treatment)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(**sensitizers** and secretagogues; thiazolidinedione, insulin secretagogue, and .alpha.-**glucosidase inhibitor** for **diabetes** treatment)

IT 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 339-43-5, Carbutamide 631-27-6, Glyclopyramide 664-95-9, Glycyclamide 968-81-0, Acetohexamide 1156-19-0, Tolazamide 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 56180-94-0, Acarbose 72432-03-2, Miglitol 74772-77-3, Ciglitazone 80879-63-6, Emiglitate 93479-97-1, Glimepiride **97322-87-7, Troglitazone** 109229-58-5, Englitazone 111025-46-8, Pioglitazone 122320-73-4 135062-02-1, Repaglinide 155141-29-0
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinedione, insulin secretagogue, and .alpha.-**glucosidase inhibitor** for **diabetes** treatment)

L32 ANSWER 2 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:81574 CAPLUS
DN 130:134188
TI Treatment of **diabetes** with a thiazolidinedione, an insulin secretagogue, and a **biguanide**
IN Buckingham, Robin Edwin; Smith, Stephen Alistair
PA Smithkline Beecham PLC, UK
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-64
ICS A61K031-44; A61K031-155; A61K031-64; A61K031-44; A61K031-155
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9903477	A1	19990128	WO 1998-GB2110	19980716
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9884488	A1	19990210	AU 1998-84488	19980716
PRAI	GB 1997-15295		19970718		
	WO 1998-GB2110		19980716		

AB A method and compn. are disclosed for the treatment of **diabetes mellitus** and conditions assocd. with **diabetes mellitus** in a mammal. The method comprises administering an effective nontoxic and pharmaceutically acceptable amt. of an insulin **sensitizer**, an insulin secretagogue and a **biguanide** antihyperglycemic agent to a mammal in need thereof.
ST thiazolidinedione insulin secretagogue **biguanide** antidiabetic; **sensitizer** secretagogue insulin **biguanide** antidiabetic
IT Antidiabetic agents
Drug delivery systems

Tablets (drug delivery systems)
(thiazolidinedione, insulin secretagogue, and **biguanide** for **diabetes** treatment)

IT **Sulfonylureas**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinedione, insulin secretagogue, and **biguanide** for **diabetes** treatment)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**sensitizerrs** and secretagogues; thiazolidinedione, insulin secretagogue, and **biguanide** for **diabetes** treatment)

IT 56-03-1D, **Biguanide**, derivs. 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 114-86-3, Phenformin 339-43-5, Carbutamide 631-27-6, Glyclopyramide 657-24-9, Metformin 664-95-9, Glycyclamide 692-13-7, Buformin 968-81-0, Acetohexamide 1156-19-0, Tolazamide 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide
32797-92-5, Glisentide 33342-05-1, Gliquidone 74772-77-3, Ciglitazone 93479-97-1, Glimepiride **97322-87-7**, **Troglitazone** 109229-58-5, Englitazone 111025-46-8, Pioglitazone 122320-73-4 135062-02-1, Repaglinide 155141-29-0
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinedione, insulin secretagogue, and **biguanide** for **diabetes** treatment)

L32 ANSWER 3 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:81573 CAPLUS
DN 130:134187
TI Treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**
IN Buckingham, Robin Edwin; Smith, Stephen Alistair
PA Smithkline Beecham PLC, UK
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-64
ICS A61K031-44; A61K031-64; A61K031-44
CC 1-10 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9903476	A1	19990128	WO 1998-GB2109	19980716
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9884487	A1	19990210	AU 1998-84487	19980716

PRAI GB 1997-15306 19970718
WO 1998-GB2109 19980716

AB A method for the treatment of **diabetes mellitus** and conditions assocd. with **diabetes mellitus** in a mammal, which method comprises administering an effective non-toxic and

pharmaceutically acceptable amt. of an insulin **sensitizer** and a sub-maximal amt. of an insulin secretagogue, to a mammal in need thereof; and a pharmaceutical compn. for use in such method are disclosed. The insulin secretagogue is esp. **sulfonylurea**. The insulin **sensitizer** is esp. 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (I). Tablet formulations contg. I maleate are given.

ST **diabetes mellitus** treatment thiazolidinedione **sulfonylurea**; insulin **sensitizer** secretagogue treatment **diabetes**

IT **Sulfonylureas**
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(as insulin secretagogue; treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**)

IT **Diabetes mellitus**
Drug delivery systems
Mammal (Mammalia)
Tablets (drug delivery systems)
(treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**)

IT 64-77-7, Tolbutamide 94-20-2, Chlorpropamide 339-43-5, Carbutamide 968-81-0, Acetohexamide 1156-19-0, Tolazamide 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 24477-37-0, Glisolamide 25046-79-1, Glisoxepide 26944-48-9, Glibornuride 29094-61-9, Glipizide 32797-92-5, Glisentide 33342-05-1, Gliquidone 93479-97-1, Glimepiride 135062-02-1, Repaglinide
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(as insulin secretagogue; treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**)

IT 74772-77-3, Ciglitazone **97322-87-7, Troglitazone** 109229-58-5, Englitazone 111025-46-8, Pioglitazone 122320-73-4
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(as insulin **sensitizer**; treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**)

IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**sensitizers** and secretagogues; treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**)

IT 155141-29-0
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tablet contg.; treatment of **diabetes** with insulin **sensitizer** thiazolidinedione and insulin secretagogue **sulfonylurea**)

L32 ANSWER 4 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1999311405 EMBASE
TI **Troglitazone**: Antihyperglycemic activity and potential role in the treatment of type 2 **diabetes**.
AU Scheen A.J.; Lefebvre P.J.
CS Dr. P.J. Lefebvre, Department of Medicine, CHU Sart Tilman (B35), B-4000 Liege 1, Belgium. pierre.lefebvre@ulg.ac.be
SO Diabetes Care, (1999) 22/9 (1568-1577).
Refs: 94

ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; Article
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Insulin resistance is a major component of type 2 **diabetes**; therefore, an insulin **sensitizer** agent like the thiazolidinedione compound **troglitazone** is considered a very promising drug. **Troglitazone** exerts an antihyperglycemic activity in a dose-dependent manner between 200 and 600 mg/day in type 2 **diabetic** patients treated with diet alone, **sulfonylureas**, or insulin. Additive antihyperglycemic effect may also be obtained by combining **troglitazone** and metformin. The antihyperglycemic effect of **troglitazone** as monotherapy is rather modest (reduction of HbA(1c) by 0.5-1.0%), but it appears to be somewhat greater when it is combined with other antidiabetic drugs. No double-blind studies have directly compared the activity of **troglitazone** with that of **sulfonylureas** or metformin. **Troglitazone** has been shown to exert additional beneficial effects on serum lipid profile and arterial blood pressure. It may be considered as a valuable alternative in insulin-resistant (obese and hyperinsulinemic) **diabetic** patients who appear to be the best responders to the drug. However, the efficacy of **troglitazone** is challenged by its safety profile, and the risk of hepatotoxicity still remains a major concern in clinical practice.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
glucose blood level
drug efficacy
drug safety
liver toxicity: SI, side effect
insulin resistance
human
article
Drug Descriptors:
***troglitazone: AE, adverse drug reaction**
***troglitazone: DT, drug therapy**
RN (**troglitazone**) **97322-87-7**

L32 ANSWER 5 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1999182630 EMBASE
TI Switching insulin-**sensitizing** agents in patients with type 2 **diabetes** who require insulin [9].
AU Blonde L.; Sandberg M.I.; Guthrie R.D. Jr.
CS Dr. L. Blonde, Ochsner Clinic, 1514 Jefferson Highway, New Orleans, LA 70121, United States. lblonde@ochsner.org
SO Diabetes Care, (1999) 22/6 (1004-1006).
Refs: 11
ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; Letter
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
038 Adverse Reactions Titles

LA English
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
weight gain
side effect
gastrointestinal disease: SI, side effect
liver dysfunction: SI, side effect
insulin resistance
lactic acidosis: SI, side effect
human
letter
Drug Descriptors:
*insulin: CB, drug combination
*insulin: DT, drug therapy
***troglitazone: AE, adverse drug reaction**
***troglitazone: CB, drug combination**
***troglitazone: DT, drug therapy**
*metformin: AE, adverse drug reaction
*metformin: DT, drug therapy
***sulfonylurea derivative: AE, adverse drug reaction**
***sulfonylurea derivative: CB, drug combination**
***sulfonylurea derivative: DT, drug therapy**
*glucose: EC, endogenous compound
*hemoglobin a1c: EC, endogenous compound
lipid: EC, endogenous compound
placebo
RN (insulin) 9004-10-8; (**troglitazone**) **97322-87-7**;
(metformin) 1115-70-4, 657-24-9; (glucose) 50-99-7, 84778-64-3;
(hemoglobin a1c) 62572-11-6; (lipid) 66455-18-3
CN Rezulin; Glucophage

L32 ANSWER 6 OF 31 MEDLINE
AN 1999215366 MEDLINE
DN 99215366
TI Insulin-**sensitizing** agent.
AU Yamanouchi T
CS Department of Internal Medicine, University of Teikyo.
SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1999 Mar) 57 (3) 675-80. Ref: 8
Journal code: KIM. ISSN: 0047-1852.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA Japanese
EM 199907
EW 19990704
AB **Troglitazone** is a new oral insulin-**sensitizing** agent from the thiazolidinedione group of compounds that has been developed in Japan Thiazolidinediones improve the insulin sensitivity at muscle, adipose tissue and liver. The overall effectiveness of **troglitazone** seems to be less potent than is usually seen with **sulfonylureas**, however, there are good responders to **troglitazone**, in which **sulfonylurea** had failed to improve glycemia. It is frequently very effective for those who are very obese and show hyperinsulinemia. Recent reports demonstrate the good therapeutic power of **troglitazone** in combination with a **sulfonylurea** or metformin, or insulin. In future, a possibility that reduction of insulin resistance by **troglitazone** reduce cardiovascular risk will be discussed. Unfortunately, wider use has led to

recognition of potential for serious liver damage. Until now, the mechanisms of the liver toxicity has not been known. We have to monitor GOT, GPT and LDH levels as recommended.

CT Check Tags: Human; Support, Non-U.S. Gov't
Chromans: AE, adverse effects
*Chromans: TU, therapeutic use
***Diabetes Mellitus: DT, drug therapy**
English Abstract
Hypoglycemic Agents: AE, adverse effects
*Hypoglycemic Agents: TU, therapeutic use
Thiazoles: AE, adverse effects
*Thiazoles: TU, therapeutic use

RN **97322-87-7 (troglitazone)**

CN 0 (Chromans); 0 (Hypoglycemic Agents); 0 (Thiazoles)

L32 ANSWER 7 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

AN 1999237452 EMBASE

TI Recent developments in oral hypoglycemic agents.

AU Shinkai H.

CS H. Shinkai, Central Pharmaceutical Res. Inst., JT Inc., 1-1 Muracaki-cho, Takatsuki, Osaka 569-1125, Japan

SO Drug Discovery Today, (1999) 4/6 (283-288).
Refs: 60
ISSN: 1359-6446 CODEN: DDTOFS

PUI S 1359-6446(99)01331-8

CY United Kingdom

DT Journal; General Review

FS 003 Endocrinology
030 Pharmacology
037 Drug Literature Index

LA English

SL English

AB Recent large-scale studies in patients with type 2 **diabetes** have suggested that improved glycemic control will reduce the incidence and severity of chronic complications. However, it is difficult to maintain the blood glucose levels of **diabetic** patients within a narrow range. Since insulin resistance and impaired insulin secretion cause hyperglycemia in type 2 **diabetes**, both improvement of insulin resistance and compensation for defective insulin secretion are necessary.
Recently, the first insulin **sensitizer** was released, and a short-acting insulinotropic agent, which should be more convenient for strict glycemic control than **sulfonylureas**, has also been launched. This review focuses on these two new classes of hypoglycemic agents.

CT Medical Descriptors:
non insulin dependent diabetes mellitus: DT, drug therapy
disease severity
diabetes control
glucose blood level
insulin resistance
insulin release
chemical structure
review
Drug Descriptors:
*oral antidiabetic agent: DV, drug development
*oral antidiabetic agent: DT, drug therapy
*oral antidiabetic agent: PD, pharmacology
glucose: EC, endogenous compound
insulin: EC, endogenous compound
thiazolidine derivative: DV, drug development

thiazolidine derivative: PD, pharmacology
troglitazone: DV, drug development
troglitazone: PD, pharmacology
ciglitazone: DV, drug development
ciglitazone: PD, pharmacology
pioglitazone: DV, drug development
pioglitazone: PD, pharmacology
rosiglitazone: DV, drug development
rosiglitazone: PD, pharmacology
4 [4 [2 (5 methyl 2 phenyl 4 oxazolyl)ethoxy]benzyl] 3,5
isoxazolidinedione: DV, drug development
brl 48482: DV, drug development
sb 213068: DV, drug development
glibenclamide: PD, pharmacology
meglitinide: PD, pharmacology
repaglinide: PD, pharmacology
nateglinide: PD, pharmacology

RN (glucose) 50-99-7, 84778-64-3; (insulin) 9004-10-8; (**troglitazone**) **97322-87-7**; (ciglitazone) 74772-77-3; (pioglitazone) 105355-27-9, 111025-46-8; (rosiglitazone) 122320-73-4; (glibenclamide) 10238-21-8; (meglitinide) 54870-28-9; (repaglinide) 135062-02-1; (nateglinide) 105746-37-0, 105816-04-4, 105816-06-6

CN Jtt 501; Brl 48482; Sb 213068

L32 ANSWER 8 OF 31 CAPLUS COPYRIGHT 1999 ACS

AN 1999:338839 CAPLUS

DN 131:139297

TI Does metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats?

AU Katayama, Shigehiro; Kosegawa, Itaru

CS The Fourth Department of Medicine, Saitama Medical School, Saitama, 350-0495, Japan

SO Obes. NIDDM (1999), 209-214. Editor(s): Shima, Kenji. Publisher: Elsevier, Amsterdam, Neth.
CODEN: 67RKA2

DT Conference

LA English

CC 1-10 (Pharmacology)

AB Insulin resistance has been given much attention in relation to the pathogenesis of essential hypertension as well as non-insulin-dependent **diabetes mellitus** (NIDDM) and obesity. This chapter summarizes effects of hypoglycemic agents such as **sulfonylurea**, **biguanide** or the newly developed insulin **sensitizer** such as **troglitazone**, on blood pressure and presents our investigation of their hypotensive effects in an animal model of NIDDM assocd. with insulin resistance, Otsuka Long-Evans Tokushima Fatty (OLETF) rats. In our study, blood pressure increased with age, reaching 160 mmHg at 23 wk. Although metformin, **troglitazone** and glibenclamide improved glucose tolerance, the former two, but not glibenclamide, lowered blood pressure in OLETF rats. Metformin and **troglitazone** also diminished plasma triglyceride levels. Plasma membrane GLUT4 protein content was significantly augmented 1.48 times with treatment with glibenclamide and 1.32-2.0 times with administration of metformin. Plasma norepinephrine and epinephrine concns. were lower in the treated group than those in controls. These results suggest that metformin and **troglitazone**, but not glibenclamide, lower blood pressure in animal models of insulin resistance, giving further evidence for insulin **sensitizing** hypoglycemic agents' beneficial effect on blood

pressure.
ST metformin **troglitazone** hypotensive insulin resistance NIDDM
IT Antidiabetic agents
Antihypertensives
Insulin resistance
Non-insulin-dependent **diabetes mellitus**
(metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats)
IT **Sulfonylureas**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats)
IT Blood triglycerides
GLUT4 glucose transporter
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats)
IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats)
IT 657-24-9, Metformin **97322-87-7, Troglitazone**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats)
IT 51-41-2, Norepinephrine 51-43-4, Epinephrine
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(metformin or **troglitazone** ameliorate insulin resistance and lower blood pressure in OLETF rats)
IT 10238-21-8, Glibenclamide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(metformin or **troglitazone** but not glibenclamide ameliorate insulin resistance and lower blood pressure in OLETF rats)

L32 ANSWER 9 OF 31 MEDLINE DUPLICATE 1
AN 1999239982 MEDLINE
DN 99239982
TI **Troglitazone** and metformin, but not glibenclamide, decrease blood pressure in Otsuka Long Evans Tokushima Fatty rats.
AU Kosegawa I; Chen S; Awata T; Negishi K; Katayama S
CS The Fourth Department of Medicine, Saitama Medical School, Japan.
SO CLINICAL AND EXPERIMENTAL HYPERTENSION, (1999 Apr) 21 (3) 199-211.
Journal code: BP0. ISSN: 1064-1963.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
EW 19990902
AB To determine whether hypoglycemic agents such as **sulfonylureas, biguanides** and the newly developed insulin **sensitizers** such as **troglitazone,** have hypotensive effects in an animal model of non-insulin-dependent **diabetes mellitus** associated with insulin resistance, male Otsuka Long Evans Tokushima Fatty
(OLETF) rats aged 12 weeks were administered following hypoglycemic agents

or vehicle by gavage for 26 weeks; glibenclamide (5 mg/kg/day), metformin (100 mg/kg/day) and **troglitazone** (70 mg/kg/day). The gain in body weight was similar in the different groups. At 36 weeks of age, **troglitazone** significantly decreased fasting plasma glucose levels when compared to controls. The area under the curve (AUC) for insulin during glucose loading (2 g/kg, i.p.) was 50% lower in the group treated with **troglitazone**. Serum triglyceride levels in **troglitazone**-treated rats were also significantly lower than in the glibenclamide-treated group. Plasma membrane GLUT4 protein content was significantly augmented by a factor of 1.48-fold ($p<0.02$) in the glibenclamide-treated group and tended to be increased 1.32 times by administration of metformin ($p=0.06$). The systolic blood pressure increased with age in controls and the glibenclamide-treated group. In contrast, treatment with either metformin or **troglitazone** significantly decreased systolic blood pressure after the age of 29 weeks.

Plasma norepinephrine and epinephrine concentrations did not show a significant decrease in the treated group when compared with the control group. These results suggest that metformin and **troglitazone**, but not glibenclamide, lower blood pressure in an animal model of insulin resistance, providing further evidence of the beneficial effect of insulin **sensitizing** hypoglycemic agents on blood pressure.

CT Check Tags: Animal; Male
Blood Glucose: ME, metabolism
*Blood Pressure: DE, drug effects
Catecholamines: BL, blood
*Chromans: PD, pharmacology
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
***Diabetes Mellitus, Non-Insulin-Dependent: PP, physiopathology**
Glyburide: PD, pharmacology
*Hypoglycemic Agents: PD, pharmacology
Insulin: BL, blood
Insulin Resistance
Lipids: BL, blood
*Metformin: PD, pharmacology
Monosaccharide Transport Proteins: ME, metabolism
Rats
Rats, Inbred OLETF
*Thiazoles: PD, pharmacology

RN 10238-21-8 (Glyburide); 11061-68-0 (Insulin); 657-24-9 (Metformin); **97322-87-7 (troglitazone)**

CN 0 (Blood Glucose); 0 (Catecholamines); 0 (Chromans); 0 (GLUT-4 protein); 0 (Hypoglycemic Agents); 0 (Lipids); 0 (Monosaccharide Transport Proteins); 0 (Thiazoles)

L32 ANSWER 10 OF 31 MEDLINE DUPLICATE 2
AN 1999160013 MEDLINE
DN 99160013
TI The emerging role of thiazolidinediones in the treatment of **diabetes-mellitus** and related disorders.
AU Subramaniam S
CS Dr. Reddy's Research Foundation, Hyderabad, India.
SO CLINICAL AND EXPERIMENTAL HYPERTENSION, (1999 Jan-Feb) 21 (1-2) 121-36. Ref: 37
Journal code: BP0. ISSN: 1064-1963.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199907
EW 19990702
AB Type II **diabetes** is a polygenic disorder, characterized in most cases by early onset of resistance to the action of insulin. Insulin **sensitizers** belonging to the thiazolidinedione class offer the first therapeutic option specifically targeting the underlying insulin resistance. **Troglitazone** is the prototype drug of this class and has been approved for marketing in several countries. **Troglitazone** offers several benefits over traditional oral hypoglycemic agents such as **sulfonylureas** and the **biguanide** metformin. Most of these advantages are related to better control of glycemic parameters with **troglitazone** alone or when added to existing treatment. In addition, it has interesting lipid lowering activity that may be of potential benefit in reducing morbidity from cardiovascular disease among **diabetics**. However, **troglitazone** may not be the ideal insulin **sensitizer** since 20-30% of **diabetics** do not respond to it. Also, it produces liver toxicity in 2% of patients, necessitating withdrawal of the drug. A number of second generation insulin **sensitizers**, belonging to the same chemical class as **troglitazone**, are in clinical development. The role of insulin **sensitizers** in the management of **diabetes** and other diseases in which insulin resistance is an underlying feature, is likely to undergo evolution as more information is obtained from clinical studies.
CT Check Tags: Animal; Comparative Study; Human
Blood Glucose: ME, metabolism
Cardiovascular Diseases: BL, blood
Cardiovascular Diseases: CO, complications
*Cardiovascular Diseases: DT, drug therapy
Chromans: CH, chemistry
*Chromans: TU, therapeutic use
Diabetes Mellitus: BL, blood
Diabetes Mellitus: CO, complications
***Diabetes Mellitus: DT, drug therapy**
Diabetes Mellitus, Experimental: BL, blood
Diabetes Mellitus, Experimental: CO, complications
Diabetes Mellitus, Experimental: DT, drug therapy
Follow-Up Studies
Hypoglycemic Agents: CH, chemistry
*Hypoglycemic Agents: TU, therapeutic use
Insulin Resistance
Lipids: BL, blood
Mice
Thiazoles: CH, chemistry
*Thiazoles: TU, therapeutic use
Treatment Outcome
RN **97322-87-7 (troglitazone)**
CN 0 (Blood Glucose); 0 (Chromans); 0 (Hypoglycemic Agents); 0 (Lipids); 0 (Thiazoles)

L32 ANSWER 11 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:325195 CAPLUS
DN 131:138770
TI Rosiglitazone SmithKline Beecham plc
AU Jones, Richard
CS Selly Oak Hospital Department of Clinical Biochemistry, Birmingham University NHS Trust, Birmingham, B29 6JD, UK
SO Curr. Opin. Oncol., Endocr. Metab. Invest. Drugs (1999), 1(1), 65-75

CODEN: COODF2; ISSN: 1464-8466
PB Current Drugs Ltd.
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with many refs. Rosiglitazone is under development by SmithKline Beecham (SB) as a potential treatment for non-insulin dependent **diabetes mellitus** (NIDDM). The compd. acts as an agonist at the peroxisome proliferator-activated receptor (PPAR)-.gamma. receptor. Rosiglitazone, in common with the related but less potent **troglitazone** (from Sankyo), is a thiazolidinedione with insulin-**sensitizing** actions. Rosiglitazone works by preventing hyperglycemia without any propensity for hypoglycemia, reducing hyperinsulinemia, and improving insulin sensitivity, while at the same time lowering plasma levels of triglycerides and free fatty acids. A preclin. study showed that **troglitazone** is a more potent vasorelaxant than rosiglitazone, which is, in turn, more potent than any of its unconjugated metabolites. The data suggested that the vasorelaxant properties were related to calcium channel-blocking activity. The company submitted an NDA to the US FDA in Nov. 1998 for the treatment of type II **diabetes**, as both a monotherapy, and in combination with **sulfonylureas**, metformin and insulin. A six-month priority review was granted by the FDA in Jan. 1999, and according to Merrill Lynch, this indicates that the compd. could be launched by the third quarter of 1999. SB filed for European approval in Dec. 1998 for the treatment of type II **diabetes**. Merrill Lynch predicts an early 2000 approval. In Sept. 1998, Merrill Lynch forecast sales of $2 billion by 2003. Deutsche Morgan Grenfell forecast sales of $3 billion by the same year, while Lehman Brothers forecast sales of $500 million by 2002.
ST review rosiglitazone antidiabetic NIDDM
IT Peroxisome proliferator-activated receptor .gamma.
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonist; antidiabetic rosiglitazone for treatment of NIDDM)
IT Antidiabetic agents
(type II **diabetes**; antidiabetic rosiglitazone for treatment of NIDDM)
IT 122320-73-4, Rosiglitazone
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antidiabetic rosiglitazone for treatment of NIDDM)

L32 ANSWER 12 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:9712 CAPLUS
DN 130:61091
TI Treatment of **diabetes** with thiazolidinedione and **sulfonylurea**
IN Smith, Stephen Alistair
PA Smithkline Beecham Plc, UK
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-64
ICS A61K031-44; A61K031-64; A61K031-44
CC 1-10 (Pharmacology)
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI	WO 9857649	A1	19981223	WO 1998-EP3688	19980615
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9885392	A1	19990104	AU 1998-85392	19980615
PRAI	GB 1997-12854	19970618			
	GB 1998-6710	19980327			
	WO 1998-EP3688	19980615			

AB A method for the treatment of **diabetes mellitus** and conditions assocd. with **diabetes mellitus** in a mammal, which method comprises administering an effective nontoxic and pharmaceutically acceptable amt. of an insulin **sensitizer** and an insulin secretagogue, to a mammal in need thereof.

ST **diabetes mellitus** treatment insulin **sensitizer** secretagogue; rosiglitazone thiazolidinedione **sulfonylurea** antidiabetic

IT Antidiabetic agents
(treatment of **diabetes** with thiazolidinedione and **sulfonylurea**)

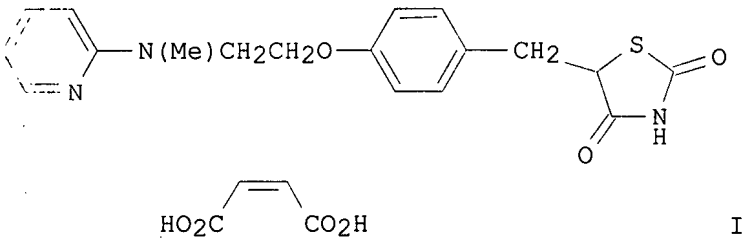
IT 64-77-7, Tolbutamide 1156-19-0, Tolazamide 9004-10-8, Insulin, biological studies 10238-21-8, Glibenclamide 21187-98-4, Gliclazide 29094-61-9, Glipizide 74772-77-3, Ciglitazone 93479-97-1, Glimepiride **97322-87-7, Troglitazone** 109229-58-5, Englitazone 111025-46-8, Pioglitazone 155141-29-0, Rosiglitazone maleate
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **diabetes** with thiazolidinedione and **sulfonylurea**)

L32 ANSWER 13 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:9698 CAPLUS
DN 130:76189
TI Treatment of **diabetes** with thiazolidinedione and alpha-**glucosidase inhibitor**
IN Smith, Stephen Alistair
PA Smithkline Beecham Plc, UK
SO PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-44
ICS A61K031-715; A61K031-70; A61K031-44; A61K031-70
CC 1-10 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9857635	A1	19981223	WO 1998-EP3691	19980615
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				

AU 9887999 A1 19990104 AU 1998-87999 19980615
PRAI GB 1997-12865 19970618
GB 1998-6708 19980327
WO 1998-EP3691 19980615

GI



I

AB A method for the treatment of **diabetes mellitus** and conditions assocd. with **diabetes mellitus** in a mammal, which method comprises administering an effective non-toxic and pharmaceutically acceptable amt. of an insulin **sensitizer** (I) and an .alpha.-**glucosidase inhibitor** antihyperglycemic agent. The effects of .alpha.-**glucosidase inhibitor** acarbose on the pharmacokinetics of I in healthy humans are described along with pharmaceutical formulations (concns. and tablets) contg. I.

ST antidiabetic thiazolidinedione alpha **glucosidase inhibitor** formulation

IT Antidiabetic agents
Tablets (drug delivery systems)
(treatment of **diabetes mellitus** and conditions assocd. with **diabetes** with thiazolidinedione deriv. and .alpha.-**glucosidase inhibitors**)

IT 56180-94-0, Acarbose 72432-03-2, Miglitol 74772-77-3, Ciglitazone 80879-63-6, Emiglitate **97322-87-7, Troglitazone** 109229-58-5, Englitazone 111025-46-8, Pioglitazone 155141-29-0
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **diabetes mellitus** and conditions assocd. with **diabetes** with thiazolidinedione deriv. and .alpha.-**glucosidase inhibitors**)

IT 9004-10-8, Insulin, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(treatment of **diabetes mellitus** and conditions assocd. with **diabetes** with thiazolidinedione deriv. and .alpha.-**glucosidase inhibitors**)

IT 9001-42-7, .alpha.-Glucosidase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of **diabetes mellitus** and conditions assocd. with **diabetes** with thiazolidinedione deriv. and .alpha.-**glucosidase inhibitors**)

L32 ANSWER 14 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1999:9697 CAPLUS
DN 130:61089
TI Treatment of **diabetes** with thiazolidinedione and metformin
IN Smith, Stephen Alistair
PA Smithkline Beecham Plc, UK
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent

LA English
IC ICM A61K031-44
ICS A61K031-155; A61K031-44; A61K031-155
CC 1-10 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9857634	A1	19981223	WO 1998-EP3690	19980615

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	AU 9885393	A1	19990104	AU 1998-85393	19980615

PRAI GB 1997-12857 19970618
GB 1998-6706 19980327
WO 1998-EP3690 19980615

AB A method for the treatment and/or prophylaxis of **diabetes mellitus**, conditions assocd. with **diabetes mellitus**, and certain complications thereof, in a mammal which method comprises administering an effective nontoxic and pharmaceutically acceptable amt. of an insulin **sensitizer** rosiglitazone (I) and a **biguanide** antihyperglycemic agent such as metformin. Pharmacokinetics of I and metformin administered alone or in combination are described. Formulations for prepg. tablets contg. I is presented.

ST thiazolidinedione antidiabetic metformin insulin **sensitizer**

IT Antidiabetic agents
Non-insulin-dependent **diabetes mellitus**
Tablets (drug delivery systems)
(treatment of **diabetes** with thiazolidinedione insulin **sensitizer** and metformin)

IT 657-24-9, Metformin 1115-70-4, Metformin hydrochloride 74772-77-3, Ciglitazone **97322-87-7**, **Troglitazone** 109229-58-5, Englitazone 111025-46-8, Pioglitazone 155141-29-0, Rosiglitazone maleate
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(treatment of **diabetes** with thiazolidinedione insulin **sensitizer** and metformin)

IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of **diabetes** with thiazolidinedione insulin **sensitizer** and metformin)

L32 ANSWER 15 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998371194 EMBASE
TI Potent inhibitory effect of **troglitazone** on carotid arterial wall thickness in type 2 **diabetes**.
AU Minamikawa J.; Tanaka S.; Yamauchi M.; Inoue D.; Koshiyama H.
CS Dr. H. Koshiyama, Division of Endocrinology/Metabolism, Department of Internal Medicine, Hyogo Prefectural Amagasaki Hospital, 1-1-1, Higashi-Daimotsu-cho, Amagasaki, Hyogo 660-0828, Japan
SO Journal of Clinical Endocrinology and Metabolism, (1998) 83/5 (1618-1820).
Refs: 20
ISSN: 0021-972X CODEN: JCEMAZ
CY United States
DT Journal; Article

FS 003 Endocrinology
006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LA English
SL English
AB There is increasing evidence that insulin resistance may be causally related to atherosclerosis. The measurement of common carotid arterial intimal and medial complex thickness (IMT) by B-mode ultrasound technique has been recognized as a powerful and non-invasive method to evaluate early atherosclerotic lesions. We investigated the effect of treatment with **troglitazone**, an insulin **sensitizer**, on IMT in a total of 135 Japanese subjects with type 2 **diabetes** **Troglitazone** (400 mg daily) was administered for 6 months in 57 patients. Compared to control group (n=78), the group given **troglitazone** showed a significant decrease in IMT as early as 3 months after the administration (IMT change -0.080[SE 0.016] mm vs. control 0.027[SE 0.007] mm, P<0.001). The decrease in IMT was also found after 6 months, although further decrease was not observed. Both HbA 1c and postprandial serum triglycerides were decreased after **troglitazone**, but there was no statistically significant relation between a decrease in IMT and those in HbAlc or postprandial triglycerides. These findings indicate that **troglitazone** has a potent inhibitory effect on progression of early atherosclerotic lesions probably through the decreased insulin resistance in type 2 **diabetes**.
CT Medical Descriptors:
***non insulin dependent diabetes mellitus: DT, drug therapy**
*carotid artery
*blood vessel diameter

***troglitazone: DT, drug therapy**
hemoglobin a1c: EC, endogenous compound
sulfonylurea: DT, drug therapy
RN (**troglitazone**) **97322-87-7**; (hemoglobin a1c) 62572-11-6

L32 ANSWER 16 OF 31 MEDLINE DUPLICATE 3
AN 1998249849 MEDLINE
DN 98249849
TI **Troglitazone**: an antidiabetic agent.
AU Chen C
CS University HealthSystem Consortium, Oak Brook, IL 60523, USA.
SO AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, (1998 May 1) 55 (9) 905-25.
Ref: 61
Journal code: CBH. ISSN: 1079-2082.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199810
EW 19981001
AB The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of **troglitazone** are reviewed. **Troglitazone** is the first oral thiazolidinedione approved for use in treating non-insulin-dependent **diabetes mellitus** (NIDDM). The drug's mechanism of action has not been fully elucidated. **Troglitazone** acts as an insulin **sensitizer**. Cell-line and animal models indicate that **troglitazone** may decrease hepatic glucose output by decreasing the rate of gluconeogenesis in the

liver or by increasing glycolysis. **Troglitazone** is rapidly absorbed after oral administration, with peak concentration occurring in two to three hours. Food increases absorption by 30-85%. The drug is extensively metabolized in the liver. **Troglitazone** has been shown to be efficacious in treating NIDDM, both as monotherapy and in combination with oral **sulfonylureas**. Patients who are obese or who have high fasting plasma insulin levels may derive the greatest benefit. Patients with impaired glucose tolerance, syndrome X, polycystic ovary syndrome, gestational **diabetes**, or Werner's syndrome may also benefit from **troglitazone**. Adverse effects, including hematologic abnormalities, liver toxicity, and hypoglycemia, have been rare in published trials; no life-threatening effects have been reported thus far. The recommended initial dosage is 200 mg once daily with meals, with an increase to 400 mg daily if satisfactory glycemic control is not achieved after two to four weeks. The average wholesale price is $348 for 100 200-mg tablets and $534 for 100 400-mg tablets. **Troglitazone** may be an effective agent for treating NIDDM, especially in patients who are obese or who have high fasting plasma insulin levels.

CT Check Tags: Human
Adult
Aged
Antihypertensive Agents: PK, pharmacokinetics
Antihypertensive Agents: TU, therapeutic use
Biological Availability
Chromans: PK, pharmacokinetics
*Chromans: TU, therapeutic use
Controlled Clinical Trials
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Drug Interactions
Drug Therapy, Combination
Hypoglycemic Agents: PK, pharmacokinetics
*Hypoglycemic Agents: TU, therapeutic use
Insulin: TU, therapeutic use
Thiazoles: PK, pharmacokinetics
*Thiazoles: TU, therapeutic use
Vasodilator Agents: TU, therapeutic use

RN 11061-68-0 (Insulin); **97322-87-7 (troglitazone)**

CN 0 (Antihypertensive Agents); 0 (Chromans); 0 (Hypoglycemic Agents); 0 (Thiazoles); 0 (Vasodilator Agents)

L32 ANSWER 17 OF 31 BIOSIS COPYRIGHT 1999 BIOSIS DUPLICATE 4

AN 1999:136013 BIOSIS

DN PREV199900136013

TI Complementary measures for promoting insulin sensitivity in skeletal muscle.

AU McCarty, M. F. (1)

CS (1) Nutrition 21, 1010 Turquoise Street, Suite 335, San Diego, CA 92109 USA

SO Medical Hypotheses, (Dec., 1998) Vol. 51, No. 6, pp. 451-464. ISSN: 0306-9877.

DT General Review

LA English

AB Insulin resistance of skeletal muscle is fundamental to both syndrome X and its frequent sequel, type II **diabetes**. In these disorders, excessive exposure of muscle to free fatty acids (FFAs) and their metabolic derivatives appears to play a prominent role in the induction of insulin resistance. Recent evidence suggests that activation of novel isoforms of protein kinase C (PKC) by diacylglycerol may mediate at least part of the adverse impact of FFAs on muscle insulin sensitivity. Vitamin E and fish oil omega-3s, by promoting the activity of diacylglycerol

kinase and inhibiting that of phosphatidate phosphohydrolase, should reduce diacylglycerol levels, thus accounting for their documented favorable impact on insulin sensitivity. Thiazolidinediones such as **troglitazone**, on the other hand, appear to intervene in the signaling pathway whereby PKC down-regulates insulin function. The insulin-**sensitizing** activity of chromium picolinate may be attributable, at least in part, to increased expression of insulin receptors. In combination with lifestyle modifications which reduce FFA exposure - weight loss, very-low-fat eating, excessive training - these measures can be expected to work in a complementary way to promote increased numbers of insulin receptors that are more functionally competent. As these measures appear to be safe and well-tolerated, they may have utility for the prevention of **diabetes** as well as its therapy. When they do not prove sufficient to achieve optimal glycemic control, excessive hepatic glucose output and impaired cell response to glucose can be addressed with metformin and **sulfonylureas**, respectively. The prospects for a rational medical management of type II **diabetes**, obviating the need for **injectible** insulin, have never been brighter.

CC Endocrine System - General *17002
Biochemical Studies - General *10060
Enzymes - General and Comparative Studies; Coenzymes *10802
Metabolism - Metabolic Disorders *13020
Muscle - General; Methods *17501

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Muscular System (Movement and Support)

IT Parts, Structures, & Systems of Organisms
adipocytes; beta cells: endocrine system; liver: digestive system; skeletal muscles: muscular system

IT Diseases
syndrome X: heart disease; type II **diabetes**: endocrine disease/pancreas, metabolic disease

IT Chemicals & Biochemicals
chromium; diacylglycerol; fish-oil; free fatty acids; protein kinase C; **troglitazone**; vanadium; vitamin E

IT Alternate Indexing
Diabetes Mellitus, Non-Insulin-Dependent (MeSH); Syndrome X (MeSH)

IT Miscellaneous Descriptors
disease management; excessive training; glycemic control; insulin resistance; insulin sensitivity; very-low-fat eating; weight loss

RN 9004-10-8 (INSULIN)
141436-78-4 (PROTEIN KINASE C)
97322-87-7 (**TROGLITAZONE**)
7440-47-3 (CHROMIUM)
1406-18-4 (VITAMIN E)
7440-62-2 (VANADIUM)

L32 ANSWER 18 OF 31 MEDLINE DUPLICATE 5
AN 1999060493 MEDLINE
DN 99060493
TI Management of obesity in NIDDM (non-insulin-dependent **diabetes mellitus**).
AU Cheah J S
CS Department of Medicine, National University Hospital, Singapore.
SO SINGAPORE MEDICAL JOURNAL, (1998 Aug) 39 (8) 380-4. Ref: 29
Journal code: URI. ISSN: 0037-5675.
CY Singapore
DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
EM 199902
EW 19990204
AB Obesity is common in NIDDM; in a cohort of 314 **diabetics** in Singapore, 44.3% are overweight. Management of obesity in **diabetics** differs from that in non-**diabetics** in that it is more urgent; weight maintenance is more difficult and hypoglycaemic medication may cause weight changes. Like in the non-**diabetic**, management of obesity in **diabetic** requires a pragmatic and realistic approach. A team approach is required: the help of the nurse educator, the dietitian, behaviour modification therapist, exercise therapist etc are required. A detailed history, careful physical examination and relevant investigations are required to assess the severity of the **diabetic** state and to exclude an occasional underlying cause of the obesity in the obese NIDDM. Weight loss is urgent in the obese NIDDM, especially those with android obesity. There must be a reduction in caloric intake. Weight loss leads to improvement in the glucose tolerance, insulin sensitivity, reduction in lipid levels and fall in blood pressure in the hypertensive. Exercise is of limited value except in the younger obese NIDDM. Metformin is the hypoglycaemic drug of choice as it leads to consistent weight reduction. The sulphonylureas may cause weight gain. Insulin should be avoided where possible as it causes further weight gain. Other hypoglycaemic agents include Glucobay (alpha-**glucosidase inhibitor**) and **Troglitazone** (insulin **sensitizer**) which do not alter the weight. Orlistat (lipase inhibitor) is promising as it causes reduction of weight, blood-glucose and lipid levels. Anti-obesity drugs (noradrenergic and serotonergic agents) have modest effects on weight reduction in the obese NIDDM; a widely use preparation, Dexfenfluramine (Adifax) has been withdrawn because of side effects. Surgery such as gastric plication is the last resort in treating the morbidly obese NIDDM. The discovery of leptin in 1994 has led to intense research into energy homeostasis in obesity; hopefully this will lead to better treatment of obesity in **diabetics** and non-**diabetics**.
CT Check Tags: Human
Anti-Obesity Agents: AE, adverse effects
Anti-Obesity Agents: TU, therapeutic use
Body Weight
Cohort Studies
***Diabetes Mellitus, Non-Insulin-Dependent: CO, complications**
Diabetes Mellitus, Non-Insulin-Dependent: PP, physiopathology
Energy Intake
Energy Metabolism
Hypoglycemic Agents: AE, adverse effects
Hypoglycemic Agents: TU, therapeutic use
Obesity: CO, complications
*Obesity: TH, therapy
Patient Care Team
Weight Loss
CN 0 (Anti-Obesity Agents); 0 (Hypoglycemic Agents)

L32 ANSWER 19 OF 31 MEDLINE DUPLICATE 6
AN 1998249695 MEDLINE
DN 98249695
TI [The present and future of treatment with oral antidiabetic agents].

Soucasnost a blizka budoucnost lecby peroralnimi antidiabetiky.
AU Rybka J
CS Interni klinika IPVZ, Batova nemocnice, Spolupracujici centrum SZO pro studium diabetu, Zlin.
SO CASOPIS LEKARU CESKYCH, (1998 Mar 9) 137 (5) 137-44. Ref: 41
Journal code: CPY. ISSN: 0008-7335.
CY Czech Republic
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Czech
EM 199808
EW 19980804
AB Oral antidiabetics (PAD) are still the most frequent pharmacotherapeutic intervention in NIDDM, characterized by insulin deficiency and in particular by insulin resistance in the liver and peripheral tissues. Depending on the site of action, they are divided into substances retarding carbohydrate breakdown in the small intestine (alpha-**glucosidase inhibitors**), substances stimulating B-cells of the islets of Langerhans (beta-cytotropic substances) and substances acting in the periphery. The authors discuss PAD, in particular SU and **biguanides** which have been used for treatment for some years and more recent preparations--acarbose (Glucobay) and miglitol. Attention is paid to perspective preparation which are in the research stage, among them in particular **troglitazone** which belongs into the group of substances which improve the sensitivity of insulin receptors (insulin **sensitizers**) which will soon be on the market. As to other possibilities the authors discuss the role of fatty acid oxidation and its inhibitors and new non-sulphonyl urea insulin secretagogues. All these preparations, despite certain limitations, offer exciting therapeutic perspectives. Further research will reveal to what extent this potential can be implemented in practice.
CT Check Tags: Human
Administration, Oral
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
English Abstract
*Hypoglycemic Agents: AD, administration & dosage
Hypoglycemic Agents: TU, therapeutic use
CN 0 (Hypoglycemic Agents)

L32 ANSWER 20 OF 31 MEDLINE DUPLICATE 7
AN 1999042415 MEDLINE
DN 99042415
TI Type 2 **diabetes**: glycemic targets and oral therapies for older patients.
AU Lardinois C K
CS University of Nevada School of Medicine, USA.
SO GERIATRICS, (1998 Nov) 53 (11) 22-3, 27-8, 33-4 passim. Ref: 29
Journal code: FO1. ISSN: 0016-867X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199902
EW 19990204
AB In older patients with type 2 **diabetes**, life expectancy and the presence of microvascular complications determine the appropriate intensity of glucose control. The available antidiabetic agents offer many

options for achieving glycemic targets, based on the needs of the individual patient. New stimulators of insulin secretion include glimepiride (a **sulfonylurea**) and repaglinide (a meglitinide). The **biguanide** metformin is especially useful in obese, insulin-resistant patients. Alpha-**glucosidase inhibitors** such as acarbose and miglitol act locally in the GI tract to reduce postprandial excursion in glucose levels. The insulin-**sensitizing** drug **troglitazone** enhances insulin-mediated glucose disposal. When **troglitazone** is used, careful monitoring of patients' liver function is required.

CT Check Tags: Human
Age Factors
Aged
Blood Glucose: AN, analysis
Carbamates: TU, therapeutic use
Diabetes Mellitus, Non-Insulin-Dependent: CO, complications
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Diabetes Mellitus, Non-Insulin-Dependent: ME, metabolism
Glucosamine: AA, analogs & derivatives
Glucosamine: TU, therapeutic use
Hypoglycemic Agents: CL, classification
Hypoglycemic Agents: PD, pharmacology
*Hypoglycemic Agents: TU, therapeutic use
Metformin: TU, therapeutic use
Piperidines: TU, therapeutic use
Sulfonylurea Compounds: TU, therapeutic use
Trisaccharides: TU, therapeutic use

RN 135062-02-1 (AG-EE 388 ZW); 3416-24-8 (Glucosamine); 56180-94-0 (acarbose); 657-24-9 (Metformin); 72432-03-2 (miglitol); 93479-97-1 (glimepiride)

CN 0 (Blood Glucose); 0 (Carbamates); 0 (Hypoglycemic Agents); 0 (Piperidines); 0 (**Sulfonylurea** Compounds); 0 (Trisaccharides)

L32 ANSWER 21 OF 31 MEDLINE

AN 1998095948 MEDLINE

DN 98095948

TI Combination therapy of insulin **sensitizer** and **sulfonylurea**.

AU Hari J

CS Department of Internal Medicine, Hyogo Prefectural Kakogawa Hospital.

SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1997 Nov) 55 Suppl 197-203. Ref: 14
Journal code: KIM. ISSN: 0047-1852.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA Japanese

EM 199805

EW 19980503

CT Check Tags: Human
Blood Glucose: ME, metabolism
*Chromans: AD, administration & dosage
Chromans: PD, pharmacology
Clinical Trials, Phase III
Diabetes Mellitus, Non-Insulin-Dependent: BL, blood
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Double-Blind Method
Drug Interactions
Drug Therapy, Combination
Hemoglobin A, Glycosylated: ME, metabolism

*Hypoglycemic Agents: AD, administration & dosage
Hypoglycemic Agents: PK, pharmacokinetics
Protein Precursors: ME, metabolism
***Sulfonylurea Compounds: AD, administration & dosage**
Sulfonylurea Compounds: PK, pharmacokinetics
*Thiazoles: AD, administration & dosage
Thiazoles: PD, pharmacology
RN 111025-46-8 (pioglitazone); **97322-87-7 (troglitazone)**
CN 0 (pre-hemoglobin A, glycosylated); 0 (Blood Glucose); 0 (Chromans); 0 (Hemoglobin A, Glycosylated); 0 (Hypoglycemic Agents); 0 (Protein Precursors); 0 (**Sulfonylurea** Compounds); 0 (Thiazoles)

L32 ANSWER 22 OF 31 MEDLINE
AN 1998095947 MEDLINE
DN 98095947
TI Alpha-**glucosidase inhibitor** and insulin **sensitizer** combination therapy in NIDDM.
AU Kitaoka H
CS First Department of Internal Medicine, Osaka Medical College.
SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1997 Nov) 55 Suppl 192-6. Ref: 15
Journal code: KIM. ISSN: 0047-1852.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
EM 199805
EW 19980503
CT Check Tags: Animal; Human
*alpha-Glucosidases: AI, antagonists & inhibitors
*Chromans: AD, administration & dosage
***Diabetes Mellitus, Non-Insulin-Dependent: DT, drug therapy**
Diabetes Mellitus, Non-Insulin-Dependent: PP, physiopathology
Drug Therapy, Combination
*Hypoglycemic Agents: AD, administration & dosage
*Inositol: AA, analogs & derivatives
Inositol: AD, administration & dosage
Insulin Resistance
*Thiazoles: AD, administration & dosage
*Trisaccharides: AD, administration & dosage
RN 111025-46-8 (pioglitazone); 56180-94-0 (acarbose); 6917-35-7 (Inositol); 83480-29-9 (voglibose); **97322-87-7 (troglitazone)**
CN EC 3.2.1.20 (alpha-Glucosidases); 0 (Chromans); 0 (Hypoglycemic Agents); 0
(Thiazoles); 0 (Trisaccharides)

L32 ANSWER 23 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 97247244 EMBASE
DN 1997247244
TI New concepts for treatment of non-insulin-dependent **diabetes mellitus**.
AU Larkins R.G.
CS R.G. Larkins, Department of Medicine, University of Melbourne, Royal Melbourne Hospital, Melbourne, Vic. 3050, Australia
SO Trends in Endocrinology and Metabolism, (1997) 8/5 (187-191).
Refs: 45
ISSN: 1043-2760 CODEN: TENME4
PUI S 1043-2760(97)00037-4
CY United States
DT Journal; General Review

FS 003 Endocrinology
037 Drug Literature Index
LA English
SL English
AB Non-insulin-dependent **diabetes mellitus** remains a major cause of morbidity and premature mortality in our community. Although potentially amenable to control by lifestyle modification, this is difficult to achieve in practice. Additional approaches using drugs that enhance insulin secretion, suppress hepatic glucose production, and increase insulin sensitivity are available, and new agents are being developed. The thiazolidinedione drugs hold particular promise as insulin-**sensitizing** agents; however, at present, insulin administration is often also required. The importance of detection and treatment of risk factors for cardiovascular disease and the earlier detection and management of microvascular and infective complications remain of crucial importance.
CT Medical Descriptors:
***maternal diabetes mellitus: DI, diagnosis**
***maternal diabetes mellitus: DT, drug therapy**
***maternal diabetes mellitus: TH, therapy**
***non insulin dependent diabetes mellitus: DT, drug therapy**
***non insulin dependent diabetes mellitus: DI, diagnosis**
***non insulin dependent diabetes mellitus: TH, therapy**
comorbidity
coronary risk
diabetic diet
glucose utilization
human
insulin release
kinesiotherapy
newborn morbidity
prematurity
priority journal
review
treatment planning
Drug Descriptors:
2,4 thiazolidinedione derivative: DT, drug therapy
alpha glucosidase inhibitor: DT, drug therapy
biguanide derivative: DT, drug therapy
insulin: DT, drug therapy
sulfonylurea: DT, drug therapy
troglitazone: DT, drug therapy
RN (insulin) 9004-10-8; (**troglitazone**) **97322-87-7**

L32 ANSWER 24 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 97296798 EMBASE
DN 1997296798
TI Antidiabetic actions of insulin **sensitizer** alone or in combination with .alpha.-**glucosidase inhibitor** in genetically obese-**diabetic** rats, Wistar fatty.
AU Odaka H.; Sano Y.; Amano N.; Ikeda H.
CS H. Odaka, Pharmaceutical Research Lab. II, Pharmaceutical Research Division, Takeda Chemical Industries Ltd., Osaka, Japan
SO Japanese Pharmacology and Therapeutics, (1997) 25/2 (35-41).
Refs: 11
ISSN: 0386-3603 CODEN: YACHDS
CY Japan
DT Journal; Article
FS 003 Endocrinology
022 Human Genetics

030 Pharmacology
037 Drug Literature Index
LA Japanese
SL English; Japanese
AB The antidiabetic actions of insulin **sensitizer**, pioglitazone .cntdot. HCl, or **troglitazone**, alone or in combination with .alpha.-**glucosidase inhibitor**, voglibose, were investigated in genetically obese-**diabetic** rats, Wistar fatty. Fourteen to 19-week-old, male Wistar fatty rats were orally administered with pioglitazone .cntdot. HCl (1 mg/kg/day) or **troglitazone** (30 mg/kg/day) alone or in combination with voglibose (5 ppm) for 14 days. Fatty rats showed hyperglycemia and hypertriglyceridemia; both plasma glucose and triglyceride levels were over 350 mg/dl. Pioglitazone .cntdot. HCl decreased plasma glucose and triglyceride to the level 61 and 45% of control, respectively. Voglibose was less effective on these plasma components. However, when combined with pioglitazone .cntdot. HCl voglibose normalized the plasma glucose level (41% of control, 144 mg/dl) and markedly decreased plasma triglyceride level (33% of control, 120 mg/dl). On the other hand, **troglitazone** showed less effect on plasma glucose (78% of control) and triglyceride (69% of control) levels. **Troglitazone** in combination with voglibose, however, markedly decreased plasma glucose to the level 48% of control, but did not induce a further decrease in plasma triglyceride. An oral glucose tolerance test performed on day 15 revealed that the glucose intolerance in fatty rats was not improved by pioglitazone .cntdot. HCl or **troglitazone** alone, but was markedly ameliorated by the combined treatment with voglibose. These results indicate that the combined treatment of pioglitazone .cntdot. HCl with voglibose shows the most potent effect to suppress hyperglycemia and to improve glucose intolerance in wistar fatty rats. On the other hand, antidiabetic activity of **troglitazone** which is 1/30 or less than that of pioglitazone .cntdot. HCl is also enhanced by the combination with voglibose in fatty rats.
CT Medical Descriptors:
***diabetes mellitus**
*obesity
animal experiment
animal model
article
controlled study
drug effect
drug screening
glucose blood level
glucose intolerance
hyperglycemia
hypertriglyceridemia
male
nonhuman
oral drug administration
oral glucose tolerance test
rat
triacylglycerol blood level
Drug Descriptors:
*pioglitazone: DV, drug development
*pioglitazone: PD, pharmacology
*pioglitazone: CB, drug combination
***troglitazone: PD, pharmacology**
***troglitazone: DV, drug development**
***troglitazone: CB, drug combination**
*voglibose: PD, pharmacology

*voglibose: DV, drug development
*voglibose: CB, drug combination
alpha glucosidase inhibitor: CB, drug combination
alpha glucosidase inhibitor: PD, pharmacology
alpha glucosidase inhibitor: DV, drug development
glucose: EC, endogenous compound
triacylglycerol: EC, endogenous compound
RN (pioglitazone) 105355-27-9, 111025-46-8; (**troglitazone**) **97322-87-7**; (voglibose) 112653-29-9, 83480-29-9; (glucose) 50-99-7, 84778-64-3
CO Takeda (Japan)

L32 ANSWER 25 OF 31 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:546304 BIOSIS
DN PREV199699268660
TI New drugs for **diabetes**.
AU Standl, Eberhard
CS Inst. Diabetes Res., Academic Hosp. Schwabing, Koelner Platz 1, D-80804 Munich Germany
SO Marshall, S. M. [Editor]; Home, P. D. [Editor]; Rizza, R. A. [Editor]. Diabetes Annual, (1996) Vol. 10, pp. 225-249. Diabetes Annual. Publisher: Elsevier Science Publishers B.V. PO Box 211, Sara Burgerhartstraat 25, 1000 AE Amsterdam, Netherlands. ISSN: 0168-9282. ISBN: 0-444-82426-X.
DT Book
LA English
CC Biochemical Studies - General 10060
Enzymes - Chemical and Physical *10806
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Carbohydrates *13004
Metabolism - Metabolic Disorders *13020
Endocrine System - Pancreas *17008
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Endocrine System *22016
BC Hominidae *86215
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Pathology; Pharmacology
IT Chemicals & Biochemicals
INSULIN; ACARBOSE; ALPHA-GLUCOSIDASE; VOGLIBOSE; MIGLITOL; **TROGLITAZONE**; GLIMEPIRIDE; REPAGLINIDE
IT Miscellaneous Descriptors
ACARBOSE; ALPHA-**GLUCOSIDASE INHIBITOR**; ANTIDIABETIC-DRUG; **BIGUANIDE** METFORMIN; BOOK CHAPTER; CLINICAL ENDOCRINOLOGY; ENDOCRINE DISEASE/PANCREAS; ENZYME INHIBITOR-DRUG; GLIMEPIRIDE; IMMUNE SYSTEM DISEASE; INSULIN **SENSITIZER**; INSULIN-DEPENDENT **DIABETES MELLITUS**; INSULIN-SECRETAGOGUE; METABOLIC DISEASE; MIGLITOL; NON-INSULIN-DEPENDENT **DIABETES MELLITUS**; PHARMACOLOGY; REPAGLINIDE; **TROGLITAZONE**; VOGLIBOSE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 9004-10-8 (INSULIN)
56180-94-0 (ACARBOSE)
9001-42-7 (ALPHA-GLUCOSIDASE)
83480-29-9 (VOGLIBOSE)

72432-03-2 (MIGLITOL)
97322-87-7 (TROGLITAZONE)
93479-97-1 (GLIMEPIRIDE)
135062-02-1 (REPAGLINIDE)

L32 ANSWER 26 OF 31 MEDLINE
AN 97071514 MEDLINE
DN 97071514
TI Drug therapy in subjects with impaired glucose tolerance.
AU Kawamori R; Yoshii H
CS Department of Medicine, Metabolism and Endocrinology, Juntendo University,
School of Medicine.
SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1996 Oct) 54 (10) 2750-3. Ref: 11
Journal code: KIM. ISSN: 0047-1852.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
EM 199704
EW 19970401
AB Since impaired glucose tolerance (IGT) is a major risk factor for non-insulin-dependent **diabetes mellitus** (NIDDM), some kinds of intervention aiming to prevent or to delay the onset of NIDDM in subjects with IGT might be considered. Besides life style modification, drug therapy which could correct insulin deficiency and insulin resistance, might prevent progression to NIDDM. One agent is an alpha-**glucosidase inhibitor**, which delays the absorption of glucose from the intestine. The resulting decrease in postprandial hyperglycemia and hyperinsulinemia could theoretically decrease insulin resistance in IGT subjects and, it is hoped, prevent or delay progression to NIDDM. Metformin, an antihyperglycemic drug of the **biguanide** class, may be effective in subjects with IGT by reducing hepatic glucose output, enhancing insulin sensitivity, or through other mechanisms such as weight loss. New insulin **sensitizers**, such as **troglitazone** and pioglitazone, improve insulin-mediated glucose disposal by enhancing tissue sensitivity to the actions of insulin and reversing the insulin resistance, characteristic of NIDDM. **Sulfonylureas** might be another candidates of drug intervention to IGT whose insulin secretory abilities are markedly reduced. As far as the question, "Can NIDDM be prevented or delayed?" is concerned, a prospective study using life style modification or above-mentioned drugs, should be performed on long-term basis.
CT alpha-Glucosidases: AI, antagonists & inhibitors
Biguanides: TU, therapeutic use
Chromans: TU, therapeutic use
Diabetes Mellitus, Non-Insulin-Dependent: ET, etiology
Diabetes Mellitus, Non-Insulin-Dependent: PC, prevention & control
English Abstract
Glucose Intolerance: CO, complications
*Glucose Intolerance: DT, drug therapy
Hypoglycemic Agents: TU, therapeutic use
Insulin Resistance
Metformin: TU, therapeutic use
Risk Factors
Sulfonylurea Compounds: TU, therapeutic use

Thiazoles: TU, therapeutic use
Trisaccharides: TU, therapeutic use
RN 111025-46-8 (pioglitazone); 56180-94-0 (acarbose); 657-24-9 (Metformin); **97322-87-7 (troglitazone)**
CN EC 3.2.1.20 (alpha-Glucosidases); 0 (**Biguanides**); 0 (Chromans); 0 (Hypoglycemic Agents); 0 (**Sulfonylurea** Compounds); 0 (Thiazoles); 0 (Trisaccharides)

L32 ANSWER 27 OF 31 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:3302 BIOSIS
DN PREV199799302505
TI **Troglitazone** (insulin **sensitizer**) not glyburide (**sulfonylurea**) improves blood pressure response to mental stress in normotensive, type II **diabetes mellitus**.
AU Sung, Bong H.; Wilson, Michael F.; Izzo., Joseph L., Jr.; Farooq, Farha; Dandona, Paresh
CS SUNY at Buffalo, Buffalo, NY USA
SO Circulation, (1996) Vol. 94, No. 8 SUPPL., pp. I215.
Meeting Info.: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Physiology, General and Miscellaneous - Stress *12008
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Carbohydrates *13004
Metabolism - Metabolic Disorders *13020
Cardiovascular System - Physiology and Biochemistry *14504
Endocrine System - Pancreas *17008
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Cardiovascular System *22010
BC Hominidae *86215
IT Major Concepts
Cardiovascular System (Transport and Circulation); Endocrine System (Chemical Coordination and Homeostasis); Metabolism; Pathology; Pharmacology; Physiology
IT Chemicals & Biochemicals
GLYBURIDE; **TROGLITAZONE**; INSULIN
IT Miscellaneous Descriptors
BLOOD PRESSURE RESPONSE; CARDIOVASCULAR MEDICINE; ENDOCRINE DISEASE/PANCREAS; GLYBURIDE; INSULIN RESISTANCE; MENTAL STRESS; METABOLIC DISEASE; METABOLIC-DRUG; METABOLISM; NON-INSULIN-DEPENDENT **DIABETES MELLITUS**; PATIENT; PHARMACOLOGY; POTENTIAL ANTIHYPERTENSIVE AGENT; **TROGLITAZONE**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 10238-21-8 (GLYBURIDE)
97322-87-7 (**TROGLITAZONE**)
9004-10-8 (INSULIN)

L32 ANSWER 28 OF 31 CAPLUS COPYRIGHT 1999 ACS
AN 1996:74096 CAPLUS
DN 124:134599
TI Thiazolidinediones

AU Whitcomb, Randall W; Saltiel, Alan R
CS Parke-Davis Pharmaceutical Research, Ann Arbor, MI, 48105, USA
SO Expert Opin. Invest. Drugs (1995), 4(12), 1299-309
CODEN: EOIDER; ISSN: 0967-8298
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 46 refs. To date, the treatment of Non-Insulin Dependent **Diabetes Mellitus** (NIDDM) has focused primarily on attempts to correct some of the metabolic abnormalities commonly assocd. with the disease. Insulin and/or insulin secretagogues, such as **sulfonylureas**, are frequently used to lower blood sugar; however, there is a significant risk of hypoglycemia. Moreover, the use of insulin or insulin secretagogues in patients who are already hyperinsulinemic may accelerate some of the cardiovascular complications of NIDDM, and further aggravate insulin resistance. Other therapeutic strategies have focused on aberrations in glucose metab. or absorption, including **biguanides**, such as metformin, or **glucosidase inhibitors**, such as acarbose. While these agents have been efficacious to a degree, they do not have a direct impact on the underlying pathol. of insulin resistance. A novel therapeutic strategy involves the use of insulin-**sensitizing** agents, such as the thiazolidinediones. These compds. appear to improve insulin resistance by enhancing insulin action in skeletal muscle, liver and adipose tissue. Recent preclin. studies have revealed key insights into the potential mechanism of action of the thiazolidinediones. Furthermore, the emerging clin. experience with one of these agents, **troglitazone**, is substantiating the benefits of these agents in insulin-resistant diseases.
ST review thiazolidinedione deriv antidiabetic
IT Antidiabetics and Hypoglycemics
(thiazolidinediones as antidiabetic agents)
IT 2295-31-0D, Thiazolidinedione, derivs.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinediones as antidiabetic agents)

L32 ANSWER 29 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 94114767 EMBASE
DN 1994114767
TI Pharmacological treatment of the obese **diabetic** patient.
AU Scheen A.J.; Lefebvre P.J.
CS Division of Diabetes, CHU Sart Tilman, Department of Medicine,B-4000 Liege 1, Belgium
SO Diabete et Metabolisme, (1993) 19/6 (547-559).
ISSN: 0338-1684 CODEN: DIMEDU
CY France
DT Journal; General Review
FS 003 Endocrinology
037 Drug Literature Index
LA English
SL English; French
AB Obesity is a well-known risk factor for non-insulin-dependent (or Type 2) **diabetes mellitus**. Consequently, reduction of weight excess comes to the front line in the prevention and management of NIDDM. It is only when diet and physical exercise fail that drug treatment should be considered. Pharmacological treatment of obesity should favour drugs

which not only promote weight loss, by reducing caloric intake and/or increasing thermogenesis and energy expenditure, but also, and especially, improve insulin sensitivity. Serotoninergic anorectic compounds (dexfenfluramine, fluoxetine) appear to possess, to some extent, all these properties. Metformin significantly reduces insulin resistance and improves glycaemic control without inducing weight gain, and even favouring some weight loss. This **biguanide** is now considered as the first line drug for the obese **diabetic** patient. Alpha-**glucosidase inhibitors** may help to reduce post-prandial glucose excursions but do not promote weight loss per se. **Sulfonylureas** can be prescribed to an obese patient when hyperglycaemia persists despite diet and the above-mentioned oral agents, but their use should be associated with reinforcement of dietary advices in order to prevent further weight increase; it is also the case for insulin therapy. Finally, drugs specifically stimulating thermogenesis and energy expenditure, new agents **sensitizing** tissues to the action of insulin and various compounds interfering with lipid metabolism are currently under extensive investigation with promising preliminary results in the obese **diabetic** patient. In conclusion, obesity remains a major problem in the management of Type 2 **diabetes mellitus** and this justifies the search for new, safe and effective, pharmacological approaches.

CT Medical Descriptors:
***diabetes mellitus: DT, drug therapy**
*obesity: DT, drug therapy
human
review
Drug Descriptors:
*amfepramone: DT, drug therapy
*dexfenfluramine: DT, drug therapy
*fenfluramine: DT, drug therapy
*fluoxetine: DT, drug therapy
*insulin: DT, drug therapy
*mazindol: DT, drug therapy
*metformin: DT, drug therapy
*phentermine: DT, drug therapy
*phenylpropanolamine: DT, drug therapy
4 [2 [(2 hydroxy 2 phenylethyl)amino]propyl]benzoic acid methyl ester hydrogen maleate
4 [2 [[2 (3 chlorophenyl) 2 hydroxyethyl]amino]propyl]phenoxyacetic acid methyl ester
acarbose: DT, drug therapy
acipimox: DT, drug therapy
alpha glucosidase inhibitor: DT, drug therapy
amphetamine: DT, drug therapy
antidiabetic agent: DT, drug therapy
antihypertensive agent: DT, drug therapy
antilipemic agent: DT, drug therapy
benfluorex: DT, drug therapy
beta adrenergic receptor stimulating agent: DT, drug therapy
caffeine: CB, drug combination
caffeine: DT, drug therapy
ciglitazone: DT, drug therapy
clofibrate: DT, drug therapy
ephedrine: DT, drug therapy
ephedrine: CB, drug combination
gemfibrozil: DT, drug therapy

magnesium: DT, drug therapy
phenmetrazine: DT, drug therapy
pioglitazone: DT, drug therapy
salbutamol: DT, drug therapy
sulfonylurea derivative: DT, drug therapy
tetrahydrolipstatin: DT, drug therapy
troglitazone
RN (amfepramone) 134-80-5, 90-84-6; (dexfenfluramine) 3239-44-9, 3239-45-0; (fenfluramine) 404-82-0, 458-24-2; (fluoxetine) 54910-89-3, 56296-78-7, 59333-67-4; (insulin) 9004-10-8; (mazindol) 22232-71-9; (metformin) 1115-70-4, 657-24-9; (phentermine) 1197-21-3, 122-09-8; (phenylpropanolamine) 14838-15-4, 154-41-6, 4345-16-8, 48115-38-4; (4 [2 [(2 hydroxy 2 phenylethyl)amino]propyl]benzoic acid methyl ester hydrogen maleate) 87857-42-9; (4 [2 [[2 (3 chlorophenyl) 2 hydroxyethyl]amino]propyl]phenoxyacetic acid methyl ester) 91097-81-3; (acarbose) 56180-94-0; (acipimox) 51037-30-0; (amphetamine) 1200-47-1, 139-10-6, 156-34-3, 2706-50-5, 300-62-9, 51-62-7, 60-13-9, 60-15-1; (benfluorex) 23602-78-0, 23642-66-2; (caffeine) 30388-07-9, 58-08-2; (ciglitazone) 74772-77-3; (clofibrate) 637-07-0; (ephedrine) 299-42-3, 50-98-6; (gemfibrozil) 25812-30-0; (magnesium) 7439-95-4; (phenmetrazine) 134-49-6, 1707-14-8, 57919-12-7; (pioglitazone) 105355-27-9, 111025-46-8; (salbutamol) 18559-94-9; (tetrahydrolipstatin) 96829-58-2; (**troglitazone**) **97322-87-7**
CN Brl 35135; Cs 045; Brl 26830a

L32 ANSWER 30 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 92240198 EMBASE
DN 1992240198
TI New oral thiazolidinedione antidiabetic agents act as insulin **sensitizers.**
AU Hofmann C.A.; Colca J.R.
CS Research Service, Hines VA Hospital,Hines, IL 60141, United States
SO Diabetes Care, (1992) 15/8 (1075-1079).
ISSN: 0149-5992 CODEN: DICAD2
CY United States
DT Journal; Note
FS 003 Endocrinology
006 Internal Medicine
037 Drug Literature Index
LA English
CT Medical Descriptors:
*insulin sensitivity
***non insulin dependent diabetes mellitus: DT, drug therapy**
drug mechanism
glucose transport
insulin release
insulin resistance
nonhuman
note
priority journal
Drug Descriptors:
***biguanide derivative: DT, drug therapy**
***sulfonylurea derivative: DT, drug therapy**
*thiazolidine derivative: DT, drug therapy
*thiazolidine derivative: PD, pharmacology
troglitazone: PD, pharmacology
troglitazone: DT, drug therapy
acetohexamide: DT, drug therapy
chlorpropamide: DT, drug therapy
ciglitazone: PD, pharmacology
ciglitazone: DT, drug therapy

englitazone: DT, drug therapy
englitazone: PD, pharmacology
glibenclamide: DT, drug therapy
metformin: DT, drug therapy
pioglitazone: DT, drug therapy
pioglitazone: PD, pharmacology
tolazamide: DT, drug therapy
tolbutamide: DT, drug therapy

RN (**troglitazone**) **97322-87-7**; (acetohexamide) 968-81-0; (chlorpropamide) 94-20-2; (ciglitazone) 74772-77-3; (englitazone) 109229-58-5; (glibenclamide) 10238-21-8; (metformin) 1115-70-4, 657-24-9; (pioglitazone) 105355-27-9, 111025-46-8; (tolazamide) 1156-19-0; (tolbutamide) 473-41-6, 64-77-7

L32 ANSWER 31 OF 31 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 93163267 EMBASE
DN 1993163267
TI Pharmacological approach in the treatment of insulin resistance.
AU Vialettes B.; Silvestre P.
CS Service de Med Interne et Nutrition, CHU La Timone, bd Jean-Moulin, F-13385 Marseille, France
SO Hormone Research, (1992) 38/1-2 (51-56).
ISSN: 0301-0163 CODEN: HRMRA3
CY Switzerland
DT Journal; Conference Article
FS 003 Endocrinology
006 Internal Medicine
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Insulin resistance syndromes are heterogeneous in either severity or mechanism. Many drugs have been shown to counteract various elements of insulin resistance. Some of them, by normalization of metabolic parameters, decrease insulin resistance induced by chronic hyperglycemia in **diabetes**. Insulin and, to some extent, **sulfonylureas** are in this group, but these drugs are not stricto sensu medication of insulin resistance. Some drugs **sensitize** peripheral tissues to the action of insulin. For instance, **biguanides** and thiazolidine-dione facilitate translocation to the membrane of glucose transporter in presence of insulin. Other compounds as vanadate or IGF-1 mimic some peripheral action of insulin. Finally, blockade of FFA oxidation by specific inhibitors (methylpalmoxyrate) can limit insulin resistance. In 1992, among these compounds, specific of insulin resistance, **biguanides** are mostly used. However, the efficacy of these drugs is moderate and limited to type 2 **diabetes**.
CT Medical Descriptors:
*insulin resistance
animal cell
animal experiment
animal model
conference paper
diabetes mellitus: DT, drug therapy
diabetes mellitus: SI, side effect
drug efficacy
drug inhibition
drug mechanism
drug sensitization
fatty acid oxidation

gene expression regulation
gene translocation
glucose blood level
glucose transport
human
human cell
hyperglycemia: CO, complication
hypoglycemia: SI, side effect
insulin blood level
mouse
nonhuman
oral drug administration
potassium channel
priority journal
rat
Drug Descriptors:
insulin receptor
*insulin: DT, drug therapy
*insulin: PD, pharmacology
troglitazone: PD, pharmacology
troglitazone: DV, drug development
aminoglycoside derivative: PD, pharmacology
beta adrenergic receptor stimulating agent: PD, pharmacology
beta adrenergic receptor stimulating agent: DV, drug development
biguanide derivative: DT, drug therapy
biguanide derivative: PD, pharmacology
ciglitazone: PD, pharmacology
ciglitazone: DV, drug development
englitazone: PD, pharmacology
englitazone: DV, drug development
glibenclamide: PD, pharmacology
gliclazide: PD, pharmacology
glucose transporter: EC, endogenous compound
immunoglobulin f(ab) fragment: PD, pharmacology
metformin: PD, pharmacology
metformin: DT, drug therapy
oral antidiabetic agent: DT, drug therapy
palmoxiric acid methyl ester: PD, pharmacology
palmoxiric acid methyl ester: DV, drug development
proinsulin: DT, drug therapy
proinsulin: AE, adverse drug reaction
propionic acid derivative: DV, drug development
propionic acid derivative: PD, pharmacology
protein tyrosine kinase: EC, endogenous compound
sulfonylurea: PD, pharmacology
thiazolidine derivative: DV, drug development
thiazolidine derivative: PD, pharmacology
tolbutamide: PD, pharmacology
vanadic acid: DV, drug development
vanadic acid: PD, pharmacology
vanadyl derivative: PD, pharmacology
vanadyl derivative: DV, drug development

RN (insulin) 9004-10-8; (**troglitazone**) **97322-87-7**; (ciglitazone) 74772-77-3; (englitazone) 109229-58-5; (glibenclamide) 10238-21-8; (gliclazide) 21187-98-4; (metformin) 1115-70-4, 657-24-9; (palmoxiric acid methyl ester) 69207-52-9; (proinsulin) 11062-00-3, 9035-68-1; (protein tyrosine kinase) 80449-02-1; (tolbutamide) 473-41-6, 64-77-7; (vanadic acid) 12260-63-8, 13981-20-9, 37353-31-4

CN Cs 045

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FILE 'USPAT' ENTERED AT 13:25:53 ON 06 OCT 1999

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  *         U. S.   P A T E N T   T E X T   F I L E                  *
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  *  THE WEEKLY PATENT TEXT AND IMAGE DATA IS CURRENT                  *
  *  THROUGH October 05, 1999.                                    *
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=> d acc 4708868 4849405 4873080 4963526 5206219 5422125 5595763 cls


4,708,868 [IMAGE AVAILABLE]    7 CLASSIFICATIONS       ANS: 1

     1.   514/309          OR
     2.   514/255          XR
     3.   514/378          XR
     4.   514/412          XR
     5.   514/471          XR
     6.   514/584          XR
     7.   514/861          XR

4,849,405 [IMAGE AVAILABLE]    1 CLASSIFICATIONS       ANS: 2

     1.   514/3            OR

4,873,080 [IMAGE AVAILABLE]    3 CLASSIFICATIONS       ANS: 3

     1.   514/315          OR
     2.   514/408          XR
     3.   514/568          XR

4,963,526 [IMAGE AVAILABLE]    4 CLASSIFICATIONS       ANS: 4

     1.   514/3            OR
     2.   514/456          XR
     3.   514/468          XR
     4.   514/963          XR

5,206,219 [IMAGE AVAILABLE]    5 CLASSIFICATIONS       ANS: 5

     1.   514/3            OR
     2.   424/455          XR
     3.   424/463          XR
     4.   424/474          XR
     5.   424/490          XR

5,422,125 [IMAGE AVAILABLE]    3 CLASSIFICATIONS       ANS: 6

     1.   424/646          OR
     2.   514/3            XR
     3.   514/866          XR

5,595,763 [IMAGE AVAILABLE]    2 CLASSIFICATIONS       ANS: 7
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     1.    424/617          OR
     2.    514/492          XR

=> e rieveley/in

E#      FILE             FREQUENCY  TERM
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E1      USPAT                    1     RIEVE, LEO S/IN
E2      USPAT                    8     RIEVE, ROBERT W/IN
E3      USPAT                    0 --> RIEVELEY/IN
E4      USPAT                    1     RIEVELEY, ROBERT B/IN
E5      USPAT                    1     RIEVEN, SHIRLEY A/IN
E6      USPAT                    1     RIEVEN, STEVE/IN
E7      USPAT                    2     RIEVES, CHERYL/IN
E8      USPAT                    1     RIEW, CHANG KIU/IN
E9      USPAT                   16     RIEW, CHANGKIU K/IN
E10     USPAT                    3     RIEW, CHANGKIU KEITH/IN
E11     USPAT                    2     RIEWALD, PAUL GORDON/IN
E12     USPAT                    1     RIEWE, DAVID PAUL/IN

=> s e4

L1            1 "RIEVELEY, ROBERT B"/IN

=> d


1.  5,955,057, Sep. 21, 1999, Effervescing or foaming bath shape or
solid; Terry W. Maunder, et al., 424/44, 43, 466; 510/447; 514/957 [IMAGE
AVAILABLE]

=> s brl 49653

          5798 BRL
             6 49653/BI
             1 49,653/BI
             7 49653
                 ((49653 OR 49,653)/BI)
L2           6 BRL 49653
                 (BRL(W)49653)

=> d 1-6


1.  5,952,356, Sep. 14, 1999, Pharmaceutical composition; Hitoshi Ikeda,
et al., 514/340, 342, 369, 376; 546/269.7, 271.4; 548/183, 226 [IMAGE
AVAILABLE]

2.  5,939,442, Aug. 17, 1999, Modulations of peroxisome proliferator
activated receptor-.gamma., and methods for the use thereof; Ronald M.
Evans, et al., 514/357, 222.2, 223.2, 226.5, 227.5, 228.8, 241, 254, 257,
365, 367 [IMAGE AVAILABLE]

3.  5,859,037, Jan. 12, 1999, Sulfonylurea-glitazone combinations for
diabetes; Randall Wayne Whitcomb, 514/369, 593, 866 [IMAGE AVAILABLE]

4.  5,814,647, Sep. 29, 1998, Use of troglitazone and related compounds
for the treatment of the climacteric symptoms; Randall J. Urban, et al.,
514/369, 252, 256, 342, 360, 375, 376 [IMAGE AVAILABLE]

5.  5,798,375, Aug. 25, 1998, Treatment of arteriosclerosis and xanthoma;
Yoshio Tsujita, et al., 514/369, 370, 510 [IMAGE AVAILABLE]

6.  5,753,681, May 19, 1998, Treatment and prophylaxis of pancreatitis;
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Toshihiko Fujiwara, et al., 514/337, 369, 370 [IMAGE AVAILABLE]

```
=> s pioglitazone

L3          36 PIOGLITAZONE

=> s troglitazone

L4          49 TROGLITAZONE

=> s mc 555

         17674 MC
         13958 555
L5           2 MC 555
                 (MC(W)555)

=> d 1-2
```

1. 4,310,793, Jan. 12, 1982, Charge/float motor vehicle electrical system; Leonard J. Sheldrake, et al., 322/28; 320/152; 322/73 [IMAGE AVAILABLE]

2. 4,271,491, Jun. 2, 1981, Intruder alarm system; Ronald R. Simpson, 367/136, 901 [IMAGE AVAILABLE]

```
=> s alrt268

L6           0 ALRT268

=> s lgd 1069

            45 LGD
          1573 1069/BI
            54 1,069/BI
          1620 1069
                 ((1069 OR 1,069)/BI)
L7           0 LGD 1069
                 (LGD(W)1069)

=> s v-411

        595796 V
         27417 411
L8           5 V-411
                 (V(W)411)

=> d 1-5
```

1. 5,814,981, Sep. 29, 1998, Voltage circuit for generating multiple stable voltages; Hiroshi Tsuchi, et al., 323/369, 298, 354 [IMAGE AVAILABLE]

2. 5,723,412, Mar. 3, 1998, 2-benzyloxy-4-phenoxypyrimidine derivative, processes for producing the derivative and herbicidal composition containing the derivative; Hisashi Kanno, et al., 504/243; 544/299, 302, 303, 309, 313, 314 [IMAGE AVAILABLE]

3. 5,561,756, Oct. 1, 1996, Textured sphere and spherical environment map rendering using texture map double indirection; Gavin S. P. Miller, et al., 345/326, 437 [IMAGE AVAILABLE]

4. 5,446,833, Aug. 29, 1995, Textured sphere and spherical environment

map rendering using texture map double indirection; Gavin S. P. Miller, et al., 345/425, 437 [IMAGE AVAILABLE]

5. 4,689,398, Aug. 25, 1987, HTLV test using synthetic peptides; Ying-Jye Wu, et al., 530/327; 930/221, DIG.811 [IMAGE AVAILABLE]

=> s pioglitazone/clm

L9 8 PIOGLITAZONE/CLM

=> d 1-8

1. 5,859,037, Jan. 12, 1999, Sulfonylurea-glitazone combinations for diabetes; Randall Wayne Whitcomb, 514/369, 593, 866 [IMAGE AVAILABLE]

2. 5,814,647, Sep. 29, 1998, Use of troglitazone and related compounds for the treatment of the climacteric symptoms; Randall J. Urban, et al., 514/369, 252, 256, 342, 360, 375, 376 [IMAGE AVAILABLE]

3. 5,708,012, Jan. 13, 1998, Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of insulin resistant subjects with normal glucose tolerance in order to prevent or delay the onset of noninsulin-dependent mellitus; Jerrold M. Olefsky, 514/337, 359, 369, 370, 439, 443, 444, 455, 456 [IMAGE AVAILABLE]

4. 5,602,133, Feb. 11, 1997, Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of disease states at risk for progressing to noninsulin-dependent diabetes mellitus; Tammy Antonucci, et al., 514/252, 256, 342, 360, 369 [IMAGE AVAILABLE]

5. 5,594,015, Jan. 14, 1997, Thiazolidine derivatives for the treatment of psoriasis; Theodore W. Kurtz, et al., 514/369, 299, 342, 367, 370 [IMAGE AVAILABLE]

6. 5,478,852, Dec. 26, 1995, Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus; Jerrold Olefsky, et al., 514/369, 252, 256, 342, 360, 375, 376 [IMAGE AVAILABLE]

7. 5,457,109, Oct. 10, 1995, Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of disease states at risk for progressing to noninsulin-dependent diabetes mellitus; Tammy Antonucci, et al., 514/252, 256, 342, 360, 369 [IMAGE AVAILABLE]

8. 5,356,913, Oct. 18, 1994, Use of insulin sensitizing agents to treat hypertension; Jerry R. Colca, 514/342, 365, 866 [IMAGE AVAILABLE]

=> s troglitazone/clm

L10 13 TROGLITAZONE/CLM

=> d 1-13

1. 5,925,657, Jul. 20, 1999, Use of PPAR.gamma. agonists for inhibition of inflammatory cytokine production; Brian Seed, et al., 514/369, 340, 365, 366, 370 [IMAGE AVAILABLE]

2. 5,859,037, Jan. 12, 1999, Sulfonylurea-glitazone combinations for diabetes; Randall Wayne Whitcomb, 514/369, 593, 866 [IMAGE AVAILABLE]

3. 5,837,255, Nov. 17, 1998, Method of reducing blood glucose by administering Harunganin or Vismin; Wayne DeWald Inman, et al.,

424/195.1; 514/3, 4, 323, 369, 635, 680, 884; 552/271 [IMAGE AVAILABLE]

4. 5,814,647, Sep. 29, 1998, Use of troglitazone and related compounds for the treatment of the climacteric symptoms; Randall J. Urban, et al., 514/369, 252, 256, 342, 360, 375, 376 [IMAGE AVAILABLE]

5. 5,798,375, Aug. 25, 1998, Treatment of arteriosclerosis and xanthoma; Yoshio Tsujita, et al., 514/369, 370, 510 [IMAGE AVAILABLE]

6. 5,747,527, May 5, 1998, Furanoeremophilane and eremophilanolide sesquiterpenes for treatment of diabetes; Wayne D. Inman, et al., 514/453, 468 [IMAGE AVAILABLE]

7. 5,708,012, Jan. 13, 1998, Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of insulin resistant subjects with normal glucose tolerance in order to prevent or delay the onset of noninsulin-dependent mellitus; Jerrold M. Olefsky, 514/337, 359, 369, 370, 439, 443, 444, 455, 456 [IMAGE AVAILABLE]

8. 5,700,820, Dec. 23, 1997, Polymorphic forms of troglitazone having enhanced anti-diabetic activity and a process for their preparation; Krishnamurthi Vyas, et al., 514/369, 370; 548/183, 184, 191 [IMAGE AVAILABLE]

9. 5,691,386, Nov. 25, 1997, Triterpenoid compound for the treatment of diabetes; Wayne D. Inman, et al., 514/691; 568/368 [IMAGE AVAILABLE]

10. 5,674,900, Oct. 7, 1997, Terpenoid-type quinones for treatment of diabetes; Rosa P. Ubillas, et al., 514/557, 680, 866; 552/298; 562/498, 503 [IMAGE AVAILABLE]

11. 5,629,319, May 13, 1997, Hypoglycemic agent from cryptolepis; Jian Luo, et al., 514/284, 285, 410, 866, 884 [IMAGE AVAILABLE]

12. 5,594,015, Jan. 14, 1997, Thiazolidine derivatives for the treatment of psoriasis; Theodore W. Kurtz, et al., 514/369, 299, 342, 367, 370 [IMAGE AVAILABLE]

13. 5,478,852, Dec. 26, 1995, Use of thiazolidinedione derivatives and related antihyperglycemic agents in the treatment of impaired glucose tolerance in order to prevent or delay the onset of noninsulin-dependent diabetes mellitus; Jerrold Olefsky, et al., 514/369, 252, 256, 342, 360,

1. 5,837,255, Nov. 17, 1998, Method of reducing blood glucose by administering Harunganin or Vismin; Wayne DeWald Inman, et al., 424/195.1; 514/3, 4, 323, 369, 635, 680, 884; 552/271 [IMAGE AVAILABLE]

2. 5,747,527, May 5, 1998, Furanoeremophilane and eremophilanolide sesquiterpenes for treatment of diabetes; Wayne D. Inman, et al., 514/453, 468 [IMAGE AVAILABLE]

3. 5,691,386, Nov. 25, 1997, Triterpenoid compound for the treatment of diabetes; Wayne D. Inman, et al., 514/691; 568/368 [IMAGE AVAILABLE]

4. 5,674,900, Oct. 7, 1997, Terpenoid-type quinones for treatment of diabetes; Rosa P. Ubillas, et al., 514/557, 680, 866; 552/298; 562/498, 503 [IMAGE AVAILABLE]

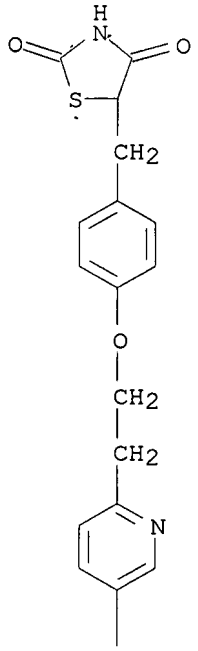
5. 5,629,319, May 13, 1997, Hypoglycemic agent from cryptolepis; Jian Luo, et al., 514/284, 285, 410, 866, 884 [IMAGE AVAILABLE]

DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, TOXLINE, TOXLIT, USAN, USPATFULL

(*File contains numerically searchable property data)

Other Sources: WHO

PAGE 1-A



PAGE 2-A

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